Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
January 30, 2013
Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center
(Rm. 1503), Silver Spring, MD

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for January 30, 2013 Meeting of the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration were approved on 2/14/13_____.

I certify that I attended the January 30, 2013 meeting of the Pulmonary-Allergy Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cindy Hong, Pharm.D.
Designated Federal Officer
Pulmonary-Allergy Drugs Advisory Committee (PADAC)

_____/s/_____
David Jacoby, M.D.
Chairperson, PADAC

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Center for Drug Evaluation and Research met on January 30, 2013 from 8 a.m. to 4 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsor, Pharmaxis. The meeting was called to order by David Jacoby, MD (Committee Chairperson); the conflict of interest statement was read into the record by Cindy Hong, PharmD (Designated Federal Officer). There were approximately 100 persons in attendance. There were nine (9) speakers for the Open Public Hearing session.

Issue: The committee discussed the new drug application (NDA) 202049, for mannitol inhalation powder (proposed trade name BRONCHITOL), for oral inhalation sponsored by Pharmaxis, for the proposed indication of management of cystic fibrosis (CF) in patients aged 6 years and older to improve pulmonary function.

Attendance:

Pulmonary-Allergy Drugs Advisory Committee Members Present (Voting): Kathryn Blake, PharmD, Paul A. Greenberger, MD, David B. Jacoby, MD (Chairperson), Rodney Mullins (Consumer Representative), Kelly Dean Stone, MD, PhD, Peter B. Terry, MD

Pulmonary-Allergy Drugs Advisory Committee Members Not Present:
Steven D. Shapiro, MD, Judith Voynow, MD

Temporary Members (Voting):
Robert Castile, MD, MS, Mary Cataletto, MD, FAAP, FCCP, John E. Connett, PhD, , Michelle S. Harkins, MD, FCCP, Amy H. Herring, ScD, Richard Parad, MD, MPH, James M. Tracy, DO, Jeffery Wagener, MD

Temporary Members (Non-Voting):
Charles Hawkins (Patient Representative)

Industry Representative to the Pulmonary-Allergy Drugs Advisory Committee (Non-Voting): Howard M. Druce, MD

FDA Participants (Non-Voting):
Badrul Chowdhury, MD, PhD, Anthony Durmowicz, MD, Kimberly Witzmann, MD, Thomas Permutt, PhD, Feng Zhou, MS

Designated Federal Officer:
Cindy Hong, Pharm.D.

Open Public Hearing Speakers:
Carroll Jenkins, Executive Director, Cystic Fibrosis Research, Inc
Emily Schaller
Moira Aitken, MD, University of Washington
Michael Boyle, MD, FCCP, Johns Hopkins Adult Cystic Fibrosis Program
Bruce Marshall, MD, Cystic Fibrosis Foundation
Gerard Cahill

Ahmet Uluer, DO, Director, Adult Cystic Fibrosis Program, Brigham and Women's Hospital and Boston Children's Hospital CF Center, Harvard Medical School
Ronnie Sharpe, cysticlife.org
Emily Grumbine

The agenda was as follows:

Call to Order Introduction of Committee	**David Jacoby, MD** Chairperson, Pulmonary-Allergy Drugs Advisory Committee (PADAC)
Conflict of Interest Statement	**Cindy Hong, PharmD** Designated Federal Officer, PADAC
Opening Remarks	**Anthony Durmowicz, MD** Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), Office of Drug Evaluation II (ODE-II), Office of New Drugs (OND), CDER, FDA
Sponsor Presentations	**Pharmaxis**
Introduction	**Ronald Dundore, PhD** VP, US Regulatory Affairs Pharmaxis
Unmet Medical Need	**Felix Ratjen, MD, PhD** Professor, Respiratory Medicine University of Toronto Hospital for Sick Children
Efficacy	**Howard Fox, MD** Chief Medical Officer Pharmaxis
Safety	**Brett Charlton, MD, PhD** Medical Director Pharmaxis
Risk/Benefit and Clinical Perspective	**Patrick Flume, MD** Professor, Pulmonary and Critical Care Medicine Medical University of South Carolina
Clarifying Questions to the Presenters	

FDA Presentations

Overview of the Clinical Program	**Kimberly Witzmann, MD** Clinical Reviewer DPARP, ODE-II, CDER, FDA
Statistical Review of Efficacy	**Feng Zhou, MS** Statistical Reviewer Division of Biostatistics II (DB-II) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
	Thomas Permutt, PhD Director, Division of Biostatistics II (DB-II) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
Clinical Review of Efficacy, Safety, and Risk/Benefit	**Kimberly Witzmann, MD**
Clarifying Questions to the Presenters	
Open Public Hearing	
Charge to the Committee	**Anthony Durmowicz, MD**
Questions to the Committee and Committee Discussion	
Questions to the Committee and Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. (**DISCUSSION)** Discuss the evidence to support the efficacy of dry powder mannitol (DPM) at a dose of 400 mg twice daily in improving pulmonary function in patients 6 years and older with cystic fibrosis.

   One member commented that currently available drugs are approved on statistical evidence of efficacy and in the case of mannitol there is no strong statistical evidence that would meet the guideline, but this drug would be first in class. In looking at the drop out rate, age separation may be very important. It was also noted that there is evidence of some efficacy, perhaps not based on statistical analyses, but it should be accepted as efficacious at least in adults.

There were comments that although a drug may not be appropriate in one person, it may be extremely beneficial in another, therefore a drug should not be ruled out because it is not efficacious in all CF patients.

One member noted that the sponsor's first study with a very small p-value was plagued with missing data, had no U.S. patients, and saw no differences in children. The second study was rid of previous issues, but it was not statistically significant.

Others also noted concern over the relatively small effect size, and the difficulty knowing the true treatment effect, given the differences in comparator groups due to drop-outs likely due to problems with tolerability.

2. **(DISCUSSION)** Discuss the overall safety profile of DPM.

Members expressed concern for high occurrence of hemoptysis in children and noted that there were higher rates of hemoptysis in the mannitol group versus the control group in the randomized trials. One member noted that the number of hemoptysis cases in the trials can not be underestimated, as hemoptysis is relatively uncommon in pediatrics and is of concern as the lungs of children are still growing and chronic irritants may lead to chronic injury to the airways.

Some committee members reported less concern for the safety profile of the drug in patients over 18 years of age. In addition, regarding safety in pediatrics, a committee member expressed that if adults were having problems with taking inhaled mannitol, they could simply discontinue treatment, but for a child or adolescent, a parent would be providing/supervising treatments, and may be less willing to discontinue for tolerability issues because they are focusing on potential benefit, and that this situation could lead to more adverse events in children, such as hemoptysis.

3. **(DISCUSSION)** Discuss the support for efficacy and the safety profile of DPM in children and adolescents 6-17 years of age.

One member commented that there is no benefit in the <18 y.o. population. Another member noted that if the sponsor is using FEV-1 as a surrogate for efficacy, then it is a poor surrogate and that there is no evidence that the quality of lives are improved on the basis of their FEV-1.

Another member expressed that in the face of a small benefit, the importance of the safety of the drug becomes more prominent, especially for patients that are desperate for a solution, and we should not provide a drug just to give patients something.

4. **(VOTE)** Considering the totality of the data, is there substantial evidence of efficacy for DPM at a dose of 400 mg twice daily for improvement of pulmonary function in patients 6 years and older with cystic fibrosis? If not, what further efficacy data should be obtained?

YES: 3 NO: 11 ABSTAIN: 0

The members voting "YES" commented that although it had missing data, the first trial reached statistical significance with a small treatment effect, as well as the second having a trend. It was also noted that adopting the modified intent to treat analysis in study 301 supported efficacy for adults, but did not appear to do so in children.

The members who voted "NO" commented that the sponsor has not met the standards of evidence for mannitol overall and future studies are required. Some expressed that there is no doubt that the drug is likely beneficial in a subset of individuals. FEV data was found to be borderline and there was no additional supporting evidence of clinical benefit. Two members stated they would have voted positively if the indication had only been for those 18 years and over.

5. **(VOTE)** Is the safety profile for DPM for the maintenance treatment of patients with cystic fibrosis sufficient to support approval? If not, what further safety data should be obtained?

YES: 3 NO: 11 ABSTAIN: 0

The members voting "YES" commented that there was sufficient weight of evidence to understand the safety profile, specifically hemoptysis which did not appear to be life-threatening and which could be managed by physicians by no longer prescribing the medication for that individual.

The members who voted "NO" commented on hemoptysis in children and the need for more information on the causes of hemoptysis, and the need for long term studies. The high level of intolerability and the drop out rate were also presented as reasons for the vote.

6. **(VOTE)** Do the efficacy and safety data provide substantial evidence to support approval of DPM at a dose of 400 mg twice daily for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function? If not, what further data should be obtained?

YES: 0 NO: 14 ABSTAIN: 0

All members voted "NO" commenting that there is no substantial efficacy and expressed concern about the risk-benefit ratio in children. Several members noted more confidence in efficacy and safety in adult population over the pediatric population.

(Please see official transcript for details.)

The meeting adjourned at approximately 3:21 p.m.